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Attar, Rubina; Wester, Axel; Koul, Sasha; Eggert, Svend; Andell, Pontus

Published in:
Open Heart

DOI (link to publication from Publisher):
10.1136/openhrt-2018-001004

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

openheart

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Rubina Attar,[1,2] Axel Wester,[1] Sasha Koul,[1] Svend Eggert,[2] Pontus Andell[3]

To cite: Attar R, Wester A, Koul S, *et al*. Peripheral artery disease and outcomes in patients with acute myocardial infarction. *Open Heart* 2019;**6**:e001004. doi:10.1136/openhrt-2018-001004

Received 3 January 2019
Revised 21 March 2019
Accepted 14 April 2019

[1]Cardiology and Clinical Sciences, Lunds Universitet, Lund, Sweden
[2]Cardiology, Aalborg University Hospital, Aalborg, Denmark
[3]Cardiology, Karolinska Institutet, Stockholm, Sweden

Correspondence to
Rubina Attar; rubina.attar@med.lu.se

ABSTRACT

Aim To describe the population of patients with previously diagnosed peripheral artery disease (PAD) experiencing a myocardial infarction (MI) and to investigate 1-year major adverse cardiac events (MACE: all-cause mortality, reinfarction, stroke and heart failure hospitalisation) following MI.

Background MI patients with PAD constitute a high-risk population with adverse cardiac outcomes. Contemporary real-life data regarding the clinical characteristics of this patient population and clinical event rates following MI remain scarce.

Methods This observational study included all MI patients presenting with ST-elevation MI or non-ST-elevation MI between 01 January 2005 and 31 December 2014 with (n=4213) and without (n=106 763) a concurrent PAD diagnosis, identified in the nationwide Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies registry and the National Patient Registry (PAD prevalence: 3.8%). Cox proportional hazard models were applied to compare the outcome between the two populations.

Results MI patients with PAD were older and more often burdened with comorbidities, such as diabetes, hypertension and previous MI. After adjustments, PAD was significantly associated with higher rates of MACE (HR 1.35, 95% CI 1.27 to 1.44), mortality (HR 1.59, 95% CI 1.43 to 1.76), reinfarction (HR 1.48, 95% CI 1.32 to 1.66), stroke (HR 1.27, 95% CI 1.05 to 1.53), heart failure (HR 1.29, 95% CI 1.20 to 1.40) and bleeding (HR 1.26, 95% CI 1.09 to 1.47) at 1 year.

Conclusion A concurrent PAD diagnosis was independently significantly associated with higher rates of adverse outcomes following MI in a nationwide real-life MI population. The low prevalence of PAD compared with previous studies suggests significant underdiagnosing. Future studies should investigate if PAD screening with ankle–brachial index may increase diagnosing and subsequently lead to improved treatment of polyvascular disease

Key Questions

What is already known about this subject?

- Previous studies have reported varying prevalences of peripheral artery disease (PAD) in a population with coronary artery disease (CAD), ranging from 8-42% depending on diagnostic method.
- It is important to identify atherosclerosis in vascular beds other than the coronary arteries, since mortality rates increase with number of arterial beds affected.

What does this study add?

- In this nationwide observational study including 110 976 patients with a myocardial infarction (MI), we found the prevalence of PAD to be 3.8%, far less than previously reported.
- Selected CAD patients with concomitant PAD had increased mortality, reinfarction, stroke, heart failure and bleeding risks.

How might this impact on clinical practice?

- The findings in this study suggests a more interdisciplinary approach when dealing with patients with poly-vascular disease.
- Individuals with known CAD may benefit from PAD screening for early disease detection.

INTRODUCTION SUMMARY

Peripheral artery disease (PAD) and coronary artery disease (CAD) are clinical manifestations of atherosclerosis involving different vascular beds. It has been established that the more arterial beds affected by atherosclerosis the higher the risk of experiencing a cardiovascular event, such as stroke, myocardial infarction (MI) or death due to cardiovascular causes.[1] Substantiating this, various studies have shown that MI patients with PAD are a high-risk population that experiences more adverse cardiac outcomes compared with MI patients without PAD.[2–7] The concurrent prevalence of PAD in patients with MI is uncertain; several studies have reported conflicting numbers ranging from 8% to 42% depending on diagnostic definition and methods.[4 5 8 9]

The interest in the role of PAD in patients with CAD has lately been rising. A major contributor has been the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, which showed that low-dose rivaroxaban two times per day plus aspirin decreased major adverse cardiac events (MACE) compared with rivaroxaban or aspirin alone in patients with PAD.[10]

Nonetheless, contemporary real-life data from large samples regarding the clinical

characteristics of MI patients with PAD remain scarce. We aimed to describe the baseline and clinical characteristics in the population of patients with PAD experiencing an MI, to analyse adverse outcomes following MI, and to investigate prescriptions of guideline-based secondary preventive medical therapies in this patient group using a nationwide contemporary population-based registry.

METHODS

Study sample

This observational follow-up study included all patients presenting with an ST-segment elevation MI (STEMI) or non-STEMI (NSTEMI) between 01 January 2005 and 31 December 2014 with and without a concurrent PAD diagnosis. The patients were identified and included from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies registry (SWEDEHEART). PAD was defined as having an electronic healthcare record of ICD-codes (10th version: I70–73; ninth version: 440–443) before baseline. In total, 4213 MI patients with a previous PAD diagnosis (prevalence: 3.8%) were compared with 106 763 MI patients without a previous PAD diagnosis.

National registries

SWEDEHEART consists of several subregistries and the ones used in this study includes the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions, which has information from coronary care units throughout the country, and the Swedish Coronary Angiography and Angioplasty Registry[11] that provides data from all catheterisation labs in Sweden. The merged SWEDEHEART registry simplifies the transferring of information between hospitals and avoids repeated entering of data in different registries as well as making high-quality data available for research purposes. The registry contains clinical information on all patients in Sweden who are treated at coronary care units, who undergo coronary angiography and percutaneous coronary interventions. Data include risk factors, past medical history, treatment during hospitalisation, discharge medications and final diagnoses. SWEDEHEART can also be connected to other registries using the unique personal number given to all Swedish citizens. We linked SWEDEHEART with the National Population Register to assess vital status and date of death, and the National Patient Registry to ascertain PAD status and comorbidities through ICD-10 diagnostic codes. The personal numbers are replaced by a serial number to ensure anonymity.[11]

Endpoints

The primary endpoint was 1-year MACE defined as all-cause mortality, rehospitalisation for MI, hospitalisation for stroke and hospitalisation for heart failure. Secondary endpoints were individual components of the primary composite endpoint at 1 year and hospitalisation for major bleeding (fatal, cerebral or bleeding requiring surgery or transfusion, defined by ICD-9 (430, 431, 432, 578, 285B, 456A, 531A, 531C, 531E, 531G, 532A, 532C, 532E, 532G, 533A, 533C, 533E, 533G, 534A, 534C, 534E, 534G and 569D) and ICD-10 (I60, I61, I62, D629, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921 and K922) codes).

Statistical analysis

Continuous variables are expressed as means with SD and differences between groups were compared using Student's t-test. Categorical variables are expressed as counts and percentages and differences between groups were analysed using the χ^2 test. Endpoints in patients with and without PAD were calculated using the Kaplan-Meier survival estimator and log-rank tests were used to calculate the differences between the groups. For reinfarction, we used a 30-day blanking period post-discharge to avoid early follow-up visits misclassified as new MIs. HRs with 95% CIs were calculated using univariable and multivariable Cox proportional hazard models. Multivariable models were adjusted for potential confounders in three models. The first model adjusted for age and sex. The second model adjusted for age, sex and comorbidities including atrial fibrillation, CAD presentation (angiographic findings and presenting symptoms), diabetes, smoking, hypertension, stroke, MI, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG), heart failure, renal failure, chronic obstructive pulmonary disease and previous bleeding. The final model adjusted for all of the above and additionally guideline-based medical therapy (dual antiplatelet therapy (DAPT), ACE inhibitor or angiotensin II receptor blocker (ACEi/ARB), beta-blockers and statins) as well as management with PCI and CABG and only included hospital survivors. The count and percentage of missing data were reported for each variable. All p values were two-tailed and a value of <0.05 was considered statistically significant. All analyses were performed using STATA V.14.0 and SPSS V.25.

RESULTS

Patient characteristics

Baseline characteristics for MI patients with and without PAD are outlined in table 1. The prevalence of PAD was 3.8% (4213/110 976). Patients with PAD were older (mean 73 vs 67 years, p<0.001), and had a heavier smoking history (more previous smokers and current smokers) (p<0.001). Moreover, a larger burden of comorbidities was seen in PAD patients, with higher prevalence's of diabetes, hypertension, hyperlipidaemia, previous MI, previous stroke, heart failure, renal failure, chronic obstructive pulmonary disease and previous bleeding (all p<0.001).

Table 1 Baseline characteristics for all MI patients with and without PAD between 2005 and 2014 in Sweden

	PAD (n=4213)	Non-PAD (n=106 763)	Entire population (n=110 976)	Missing n (%)	P value
n (%)	4213 (3.8)	106 521 (96.2)	110 734	242 (0.2)	<0.001
Age (years) mean (SD)	73.1 (8.9)	67.4 (11.5)	67.6 (11.5)		
Sex n (%)					
Male	2801 (66.5)	73 183 (68.6)	75 984 (68.5)	0	0.005
Female	1412 (33.5)	33 580 (31.5)	34 992 (31.5)		
Smoking status n (%)					
Never	978 (23.2)	41 055 (38.5)	42 033 (37.9)	5918 (5.3)	<0.001
Ex-smoker	1825 (42.3)	33 653 (31.5)	35 478 (32.0)		
(>1 month) Smoker	1104 (26.2)	26 443 (24.8)	27 547 (24.8)		
Diabetes n (%)	1584 (37.7)	22 077 (20.7)	23 664 (21.3)	0	<0.001
Hypertension n (%)	3543 (84.1)	59 561 (55.8)	63 104 (56.9)	1241 (1.2)	<0.001
Hyperlipidaemia n (%)	2286 (54.3)	24 025 (22.5)	26 311 (23.7)	1141 (1.0)	<0.001
Previous myocardial infarction n (%)	1791 (42.5)	17 072 (16.0)	18 863 (17.0)	1692 (1.6)	<0.001
Previous PCI n (%)	617 (14.7)	6431 (6.0)	7048 (6.4)	162 (0.2)	<0.001
Previous CABG n (%)	825 (19.6)	4940 (4.6)	5765 (5.2)	92 (0.1)	<0.001
Previous stroke n (%)	911 (21.6)	8360 (7.8)	9271 (8.4)	2930 (2.7)	<0.001
Heart failure n (%)	786 (18.7)	4778 (4.5)	5564 (5.0)	0	<0.001
Renal failure n (%)	445 (10.6)	1596 (1.5)	2041 (1.8)	0	<0.001
Dialysis n (%)	124 (2.9)	356 (0.3)	480 (0.4)		<0.001
COPD n (%)	617 (14.7)	5378 (5.0)	5995 (5.4)	0	<0.001
Previous bleeding n (%)	427 (10.1)	4053 (3.8)	4480 (4.0)	0	<0.001

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Clinical findings and presentation

The laboratory findings, clinical presentations, ECG changes and procedural characteristics during hospitalisation for MI patients with and without PAD are outlined in table 2. The laboratory findings showed that patients with MI and PAD had higher levels of C reactive protein and creatinine and lower levels of haemoglobin. Patients with PAD were more likely to present with dyspnoea compared with patients without PAD. They also had slightly lower blood pressure and higher heart rate compared with the non-PAD group at presentation. Moreover, the PAD group experienced more NSTEMI than STEMI, and their presenting ECG showed more atrial fibrillation or flutter and more bundle branch block. PAD patients had more severe CAD with more multivessel and left main disease on the angiogram and they had lower left ventricular function. The PAD group were less often revascularised with PCI or CABG compared with the non-PAD group. All differences presented have a p value of <0.05.

Discharge medications

Patients with MI and PAD were less frequently discharged with DAPT as seen in table 3. In contrast, these patients were more often discharged with anticoagulants, such as warfarin, as atrial fibrillation was more common. There were no clinically relevant differences in prescriptions of ACEi/ARB, beta-blockers or statins. MI and PAD patients more often received digoxin and diuretics.

Clinical endpoints

The primary endpoint of 1-year MACE occurred significantly more frequently in the PAD group compared with the non-PAD group with an unadjusted HR of 2.65 (95% CI 2.52 to 2.78) (table 4 and figure 1). Following adjustment for age and sex, the HR decreased to 2.09 (95% CI 1.98 to 2.20). Further adjustment for comorbidities decreased the HR to 1.31 (95% CI 1.21 to 1.42). Adjustments for guideline-based medical therapy and management with PCI and CABG increased the HR to 1.35 (95% CI 1.27 to 1.44). The adjusted secondary endpoints, mortality (HR 1.59, 95% CI 1.43 to 1.76), reinfarction (HR 1.48, 95% CI 1.32 to 1.66), stroke (HR 1.27, 95% CI 1.05 to 1.53), heart failure (HR 1.29, 95% CI 1.20 to 1.40) and bleeding rates (HR 1.26, 95% CI 1.09 to 1.47), were significantly higher in the PAD population (table 4).

Table 2 Laboratory findings, clinical presentation, ECG changes and procedures in the different MI groups during hospitalisation

	PAD	Non-PAD	Entire population	Missing n (%)	P value
Creatinine mean (SD)	120.0 (106.0)	88.6 (47.0)	90.0 (50.8)	4878 (4.4)	<0.001
Haemoglobin mean (SD)	132.6 (17.9)	140.7 (15.7)	140.4 (15.9)	16 228 (14.6)	<0.001
CRP mean (SD)	28.4 (50.1)	18.0 (39.6)	18.3 (40.1)	13 362 (12.0)	<0.001
Coronary marker levels mean (SD)					
Troponin T	125.4 (852)	85.4 (675)	86.8 (682)	79 943 (72.0)	0.056
Troponin I	23.5 (189)	21.5 (136)	21.6 (139)	68 354 (61.2)	0.571
Systolic blood pressure mean (SD)	145.3 (30.8)	148.4 (29.2)	148.3 (29.3)	5831 (5.3)	<0.001
Diastolic blood pressure mean (SD)	80.6 (17.2)	85.25 (17.1)	85.3 (17.2)	8766 (7.9)	<0.001
Heart rate mean (SD)	83.1 (24.3)	78.7 (21.6)	78.9 (21.7)	970 (0.9)	<0.001
Presenting symptoms n (%)					
Chest pain	3465 (82.3)	94 583 (88.6)	98 048 (88.4)	1203 (1.1)	<0.001
Dyspnoea	378 (9.0)	4392 (4.1)	4770 (4.3)		
Cardiac arrest	58 (1.4)	1325 (1.2)	1383 (1.3)		
Other	277 (6.6)	5295 (5.0)	5572 (5.0)		
Infarct type n (%)					
STEMI	1261 (29.9)	43 505 (40.8)	44 766 (40.3)	396 (0.4)	<0.001
NSTEMI	2940 (69.8)	62 874 (58.8)	65 814 (59.3)		
ECG: ST-segment n (%)					
Normal	676 (16.1)	22 161 (20.8)	22 837 (20.6)	12 915 (11.6)	<0.001
ST-elevation	1193 (28.3)	41 644 (39.0)	42 837 (38.6)		
ST-depression	1259 (29.9)	20 743 (19.4)	22 002 (19.3)		
Pathological T-wave	384 (9.1)	10 001 (9.4)	10 385 (9.4)		
ECG: rhythm n (%)					
Sinus	3470 (82.4)	95 863 (89.8)	99 333 (89.5)	3740 (3.4)	<0.001
Atrial fibrillation/flutter	545 (12.9)	7358 (6.9)	7903 (7.1)		
ECG: QRS n (%)					
Normal	2464 (58.5)	72 427 (67.8)	74 891 (67.5)	15 317 (13.8)	<0.001
LBBB	315 (7.5)	4369 (4.1)	4684 (4.2)		
RBBB	227 (5.4)	4046 (3.8)	4273 (3.9)		
Pathological Q-wave	479 (11.4)	11 332 (10.6)	11 811 (10.6)		
Left ventricular function n (%)					
Normal≥50%	1454 (34.5)	50 705 (47.5)	52 159 (47.0)	22 778 (20.5)	<0.001
Slightly decreased 40%–49%	780 (18.5)	18 770 (17.6)	19 550 (17.6)		
Moderately decreased 30%–39%	576 (13.7)	10 991 (10.3)	11 567 (10.4)		
Severely decreased <30%	350 (8.3)	4572 (4.3)	4922 (4.4)		
PCI n (%)	2846 (67.6)	82 397 (77.2)	85 243 (76.8)	0	<0.001
CABG n (%)	280 (6.7)	4247 (4.9)	5527 (5.0)	0	<0.001
Angiographic findings					
Normal/atheromatosis	208 (4.9)	9708 (9.1)	9916 (8.9)	646 (0.6)	<0.001
1-vessel, no LMD	919 (21.8)	42 138 (39.5)	43 057 (38.8)		
2-vessel, no LMD	970 (23.0)	26 096 (24.4)	27 066 (24.4)		
3-vessel, no LMD	1311 (31.1)	20 608 (19.3)	21 919 (19.8)		
LMD	756 (17.9)	7616 (7.1)	8372 (7.5)		

CABG, coronary artery bypass graft; CRP, C reactive protein;LBBB, left bundle branch block; LMD, left main disease; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI;PAD, peripheral artery disease; PCI, percutaneous coronary intervention;RBBB, right bundle branch block; STEMI, ST-segment elevation MI.

Table 3 Discharge medications (only hospital survivors)

	PAD	Non-PAD	Entire population	Missing n (%)	P value
DAPT n (%)	3050 (77.2)	87 052 (83.9)	90 102 (83.7)	294 (0.3)	<0.001
Aspirin n (%)	3686 (93.3)	99 068 (93.3)	102 754 (95.4)	134 (0.1)	<0.001
P2Y12 inhibitor n (%) types	3223 (81.5)	89 907 (86.7)	93 130 (86.5)	160 (0.2)	<0.001
Clopidogrel	2696 (68.2)	71 170 (68.6)	73 866 (68.6)		
Prasugrel	30 (0.8)	1612 (1.6)	1642 (1.5)		
Ticagrelor	473 (12.0)	16 609 (16.0)	17 082 (15.9)		
Anticoagulants n (%) types	369 (9.3)	3777 (3.6)	4146 (3.9)	725 (0.7)	<0.001
Warfarin	366 (9.3)	3700 (3.6)	4066 (3.8)		
Dabigatran	2 (0.05)	46 (0.04)	48 (0.04)		
Rivaroxaban	1 (0.03)	14 (0.01)	15 (0.01)		
ACEi/ARB n (%)	3044 (77.0)	78 897 (76.1)	81 942 (76.1)	1465 (1.4)	0.172
Beta blockers n (%)	3531 (89.3)	93 873 (90.5)	97 404 (90.5)	149 (0.1)	0.022
Calcium antagonists n (%)	1073 (27.1)	13 797 (13.3)	14 870 (13.8)	170 (0.2)	<0.001
Digitalis n (%)	151 (3.8)	1852 (1.8)	2003 (1.9)	151 (0.1)	<0.001
Diuretics n (%)	1791 (45.3)	23 446 (22.6)	25 237 (23.4)	159 (0.2)	<0.001
Statins n (%)	3556 (90.0)	96 649 (93.2)	100 205 (93.1)	161 (0.2)	<0.001
Other lipid lowering agents n (%) types	122 (3.1)	1289 (1.2)	1411 (1.3)	1193 (1.1)	<0.001
Ezetimibe	95 (2.4)	978 (0.9)	1073 (1.0)		
Fibrates	13 (0.3)	156 (0.2)	169 (0.2)		

ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; DAPT, dual antiplatelet therapy (aspirin and P2Y12 inhibitor);PAD, peripheral artery disease.

DISCUSSION

To the best of our knowledge, this is the largest registry study to date investigating the baseline and in-hospital characteristics including procedures, discharge medication as well as 1-year MACE following MI in a population with established PAD. Our main findings were significant associations between PAD and higher 1-year rates of MACE, mortality, reinfarction, stroke, heart failure and bleeding following MI. After adjustments for baseline differences including age, comorbidities and guideline-based secondary preventive medical therapies, the HR was lowered but independent statistically significant associations between PAD and higher occurrence of all endpoints

Table 4 Clinical endpoints for MI patients with PAD compared with non-PAD patients at 1 year

	Kaplan-Meier event rates (%)		Unadjusted HR	Adjusted HR (95% CI)		
End points	PAD	Non-PAD	(95% CI)	Model 1	Model 2	Model 3
MACE	0.647 (35.3)	0.852 (14.8)	2.65 (2.52 to 2.78)*	2.09 (1.98 to 2.20)*	1.31 (1.21 to 1.42)*	1.35 (1.27 to 1.44)*
Mortality	0.807 (19.3)	0.934 (6.6)	3.24 (3.00 to 3.50)*	2.38 (2.21 to 2.57)*	1.69 (1.48 to 1.91)*	1.59 (1.43 to 1.76)*
Reinfarction	0.893 (10.7)	0.959 (4.1)	2.65 (2.39 to 2.94)*	2.24 (2.02 to 2.49)*	1.23 (1.05 to 1.44)†	1.48 (1.32 to 1.66)*
Stroke	0.959 (4.1)	0.982 (1,8)	2.38 (2.01 to 2.80)*	1.86 (1.57 to 2.20)*	1.39 (1.08 to 1.79)†	1.27 (1.06 to 1.53)†
Heart failure	0.778 (22.2)	0.913 (8.7)	2.73 (2.55 to 2.94)*	2.1 (2.08 to 2.46)*	1.21 (1.09 to 1.35)*	1.29 (1.20 to 1.40)*
Bleeding	0.939 (6.1)	0.971 (2.9)	2.08 (1.81 to 2.38)*	1.72 (1.50 to 1.98)*	1.25 (1.01 to 1.56)†	1.26 (1.09 to 1.47)†

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, smoking and comorbidities (including previous PCI and CABG).
Model 3: adjusted for age, sex, smoking, comorbidities, guideline-based therapy (DAPT), ARB/ACEi, beta blockers and statins, and management with PCI and CABG.
*P<0.001.
†P<0.05.
ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy (aspirin and P2Y12 inhibitor); MACE, major adverse cardiac events; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

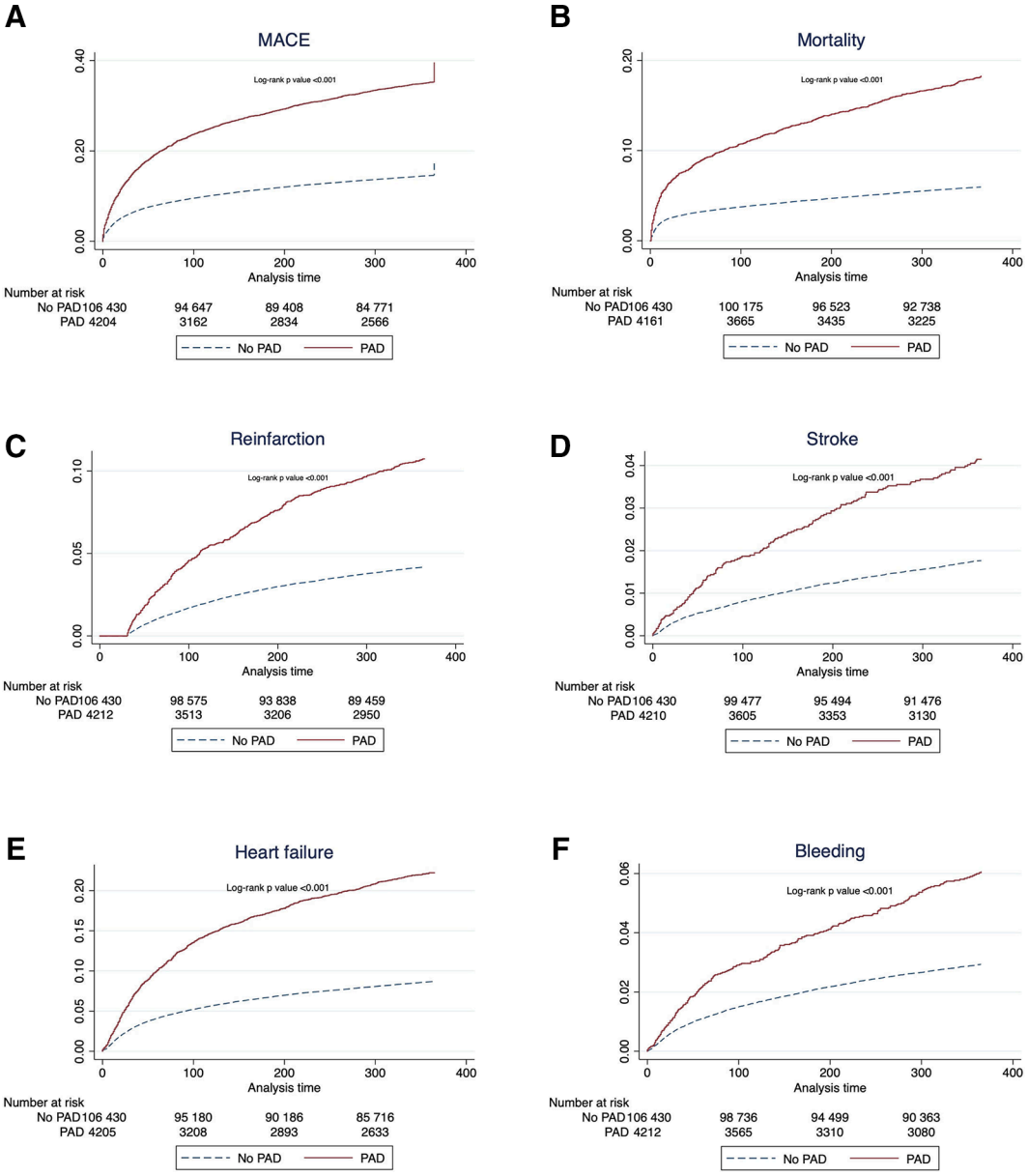

Figure 1 (A–F) Kaplan-Meier survival curves showing the crude 1-year estimates of MACE (mortality, reinfarction, stroke and heart failure), mortality, reinfarction, stroke, heart failure and bleeding rates in an MI population with and without PAD. MACE, major adverse cardiac events; MI, myocardial infarction; PAD, peripheral artery disease.

remained, indicating a high risk accompanied with PAD after MI.

Patient characteristics and clinical presentation

The prevalence of previously diagnosed PAD in the MI population was 3.8% in our study, which is lower than what previous studies have reported.[4 5 8 9] Two other studies found the PAD prevalence to be 8.2% and 13.5% in study populations of 28 771 and 4480 subjects, respectively, were relatively small-scaled compared with our study population (n=110 976). The highest prevalence of 40%[8] and 42%[9] were found in even smaller studies with 100 and 952 subjects correspondingly. The latter studies were the only studies that defined PAD by measuring the ankle–brachial index of the subjects in the clinical settings. The large differences between symptomatic PAD and PAD defined by screening with ankle–brachial index are likely explained by the relatively long subclinical asymptomatic phase of PAD before the disease manifests itself clinically. A systematic review by Fowkes *et al*,[12] pooling a total of 112 027 participants, found the prevalence of PAD in the age range between 55 and 79 years to be roughly 9.5%. Taken together, the relatively low PAD prevalence in our study reflects symptomatic PAD that has led to a clinical diagnosis, which is vastly different from subclinical PAD.

We found that patients with PAD had more cardiac risk factors, such as smoking, hypertension, hyperlipidaemia and diabetes, and were generally more comorbid, which is in accordance with previous

research.[2 7 8] A slightly lower blood pressure was seen in the PAD population; however, since blood pressure was measured peripherally, there is a possibility of false low levels due to subclavian disease in this population. Patients with PAD had higher rates of previous PCI and CABG at baseline and higher rates of CABG but lesser rates of PCI during MI hospitalisation, indicating more advanced coronary heart disease. This is further corroborated by the angiographic findings with more multivessel and left main disease in the PAD population. Our results are supported by a study that found PAD associated with more previous revascularisations.[2] Further supporting our study, results from the OPUS-TIMI study showed that PAD patients more often had severe CAD and subsequently underwent more CABG compared with PCI.[7]

Discharge medications

The PAD population was less likely to be treated with DAPT at discharge, but they were more often prescribed warfarin in line with an increased prevalence of atrial fibrillation. Newer studies have implicated that antithrombotic medications, such as ticagrelor and clopidogrel, could be advantageous as supplementing therapies in reducing the risk of cardiovascular events in patients with PAD.[10 13 14] The COMPASS PAD trial[10] concluded, for the first time, the use of rivaroxaban (2.5 mg two times per day) and aspirin as superior treatment compared with aspirin alone with reduced rates of adverse cardiac events. Another recent antithrombotic treatment alternative is prolonged treatment with low-dose ticagrelor (60 mg two times per day), which has had promising results published with regard to MI patients with concomitant PAD.[13] Yet again, these studies were published after our study period and thus, the indications were not approved during our study's time frame.

Endpoints

A prospective study by Grenon *et al*[2] including 2018 patients with stable CAD concluded an HR of 1.8 (95% CI 1.2 to 2.7) of death and an HR of 1.7 (95% CI 1.0 to 2.9) for cardiovascular events for MI patients with PAD compared with MI patients without PAD. In our study, the corresponding HRs were 1.6 and 1.4, respectively. The difference is likely explained by the different definitions of cardiovascular events compared with our term MACE. Cardiovascular events in the mentioned study were defined as stroke, transient ischaemic attack, heart failure, MI, revascularisation and death. Furthermore, their adjustment model included race, self-reported history of PAD, inflammatory biomarkers, glycaemic control and health behaviours. Various other studies confirm the increased mortality seen in our study: a follow-up study by Dinser *et al*[15] investigating 4307 patients with incident acute myocardial infarction (AMI) found the mortality HR (follow-up 5.7 years) to be 1.70 (95% CI 1.35 to 2.13) in the PAD population. Moreover, a study consisting of 4480 patients hospitalised for AMI by Spencer *et al*[5] found a 1-year mortality OR of 2.00 (95% CI 1.58 to 2.52).

The association between PAD and stroke has previously been described[16] and our results corroborate this link, suggesting that the more arterial beds affected the more likely it is that an additional atherosclerotic vascular event will occur.

Patients with PAD had a higher risk of being hospitalised for heart failure following MI. In accordance with our results, a meta-analysis established PAD as an independent predictor of adverse outcomes in patients with heart failure following MI.[4] Both PAD and heart failure are associated with a high morbidity burden. As previously shown, patients with heart failure have a higher prevalence of PAD and present with worse clinical outcomes.[17] The treatment of PAD also includes exercise,[18] which can present as a challenge in patients with heart failure due to decreased exercise capacity.[19] Thus, this vulnerable population with three severe diagnoses, PAD, MI and heart failure, represent a particularly challenging clinical scenario.

A study by Baumann *et al*[20] investigating the bleeding risk profile and HAS-BLED scores found that patients with PAD had higher risk of bleeding complications compared with the general population. We observed the same pattern in our population. Ischaemic risk and bleeding risk often increase in parallel, which our study also suggests is the case in PAD.

Clinical implication

MI patients with concomitant PAD are undoubtedly a high-risk population with a high prevalence of cardiac risk factors, challenging comorbidities and more severe CAD. There is an urgent need of a more interdisciplinary approach when dealing with this patient group. In the new guidelines of PAD management, it is pointed out that patients with CAD should be considered for PAD screening. After highlighting the various different PAD prevalences reported in our and others' studies, we agree that PAD screening should be considered in selected patients with a high likelihood of subclinical PAD in order to diagnose the disease early, and subsequently optimally tailor the treatment and provide these patients with newer efficacious medical treatment alternatives.

Limitations

All patients in our study have previously received an electronic code of PAD and this study, therefore, only entails those with a diagnosis of clinically manifested PAD. Some patients may have been excluded in the study due to various reasons relating to known limitations of registry-based studies. These include, but are not limited to, subclinical disease and underdiagnosis, patients solely managed in the primary care setting and misclassifications of ICD diagnosis codes. Accordingly, we did not have data on the severity of PAD in the population as we had no information on ankle–brachial indexes or other PAD related measurements.

CONCLUSION

In this contemporary nationwide population-based study, MI patients with concurrent PAD constituted a high-risk population that was independently and significantly associated with higher risks of MACE, all-cause mortality, reinfarction, stroke, heart failure and bleeding after MI. These patients remain a challenging patient population and there is an urgent need of a more interdisciplinary approach to improve the management of these patients. Moreover, the prevalence of PAD in this study was low compared with previous research. Future studies should investigate if PAD screening with ankle–brachial index may combat underdiagnosing, which subsequently could lead to more patients being treated with novel efficacious treatments to alleviate the increased adverse outcomes of polyvascular disease.

Contributors RA, SK and PA devised the main conceptual ideas and designed the study. RA developed the analysis plan, performed the data collection and statistical analyses as well as interpretation of the results, which SK, PA, AW and SE also contributed to. RA wrote the manuscript. SK, PA, AW and SE provided feedback and helped to shape the article. PA provided firsthand guidance throughout and critical revision of the article. All authors approved the final version of the article to be published.

Funding This study was supported by a grant from the Märta Winkler Foundation.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Swedish Central Ethics Committee, DNR: 2019-01458.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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